

Migraine frequency and risk of cardiovascular disease in women



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ABSTRACT

Background: Migraine has been associated with risk of cardiovascular disease (CVD). Data on the association between migraine frequency and CVD are sparse.

Methods: Prospective cohort study of 27,798 US women aged ≥ 45 years, who were free of CVD, and for whom we had information on lipids and migraine frequency. We categorized migraine frequency as $<$ monthly, monthly, and \geq weekly. Incident CVD was confirmed after medical record review.

Results: Of the 3,568 women with active migraine at baseline, 75.3% reported a migraine frequency of $<$ monthly, 19.7% monthly, and 5.0% \geq weekly. During 11.9 years of follow-up, 706 CVD events occurred. Compared with women without migraine, the multivariable-adjusted hazard ratios (HRs) (95% confidence intervals) among active migraineurs for CVD were 1.55 (1.22–1.97), 0.65 (0.31–1.38), and 1.93 (0.86–4.33) for an attack frequency of $<$ monthly, monthly, and \geq weekly, respectively. The association between migraine frequency and CVD was only apparent among migraineurs with aura. Among those, the multivariable-adjusted HRs for women with a migraine frequency $<$ monthly ranged from 1.81 (1.30–2.50) for coronary revascularizations to 2.43 (1.58–3.74) for myocardial infarction. For women with active migraine with aura and migraine frequencies of \geq weekly, we only found significant increased risk of ischemic stroke (HR = 4.25 [1.36–13.29]).

Conclusions: In our data, the association between migraine and cardiovascular disease varies by migraine frequency. Significant associations were only found among women with migraine with aura. Ischemic stroke was the only outcome associated with a high-attack frequency while a low-attack frequency was associated with any vascular event. Low number of outcome events should caution the interpretation. *Neurology*® 2009;73:581–588

GLOSSARY

CI = confidence interval; CVD = cardiovascular disease; HR = hazard ratio; MI = myocardial infarction; WHS = Women's Health Study.

Migraine is a primary, chronic-intermittent headache disorder that affects a large proportion of the population, predominantly women.¹ It is characterized by recurrent headache attacks, which typically are located unilaterally, of pulsating pain quality, and of moderate to severe intensity. Migraine attacks are often accompanied by sensitivity to light and sound, vomiting, or nausea. In some patients, usually prior to headache onset, transient neurologic symptoms occur known as migraine aura,² most often affecting the visual field.

A large body of literature supports an association between migraine and ischemic stroke^{3–9} that is in most studies limited to patients with migraine with aura. Recent findings from prospective cohort studies further suggest an association between migraine with aura and any vascular event, including

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myocardial infarction (MI).¹⁰⁻¹² However, the biologic mechanisms linking migraine with ischemic vascular events have yet to be established. Potential mechanisms that increase the risk for cardiovascular disease (CVD) among migraineurs include prothrombotic effects, liability to vascular risk factors, impaired vascular reactivity, specific gene variants, congenital heart defects, migraine-specific treatments, or a direct involvement of the migraine pathophysiology.^{13,14}

Moreover, it remains unclear whether migraine frequency is associated with risk of CVD. Results of previous case-control studies suggest that the risk for ischemic stroke further increases with rising attack frequency among women with migraine with aura.^{5,9} Information whether migraine frequency is associated with increased risk of major ischemic vascular events, including MI, is lacking. We thus aimed to evaluate whether the association between migraine and CVD differs according to migraine frequency in a large cohort of US female health professionals.

METHODS Study population. This was a prospective cohort study among participants in the Women's Health Study (WHS), a completed trial designed to test the benefits and risks of low-dose aspirin and vitamin E in the primary prevention of CVD and cancer among apparently healthy women. The design and results have been described in detail previously.^{15,16} Briefly, a total of 39,876 US female health professionals aged ≥ 45 years at study entry (1992 to 1995) and without a history of CVD, cancer, or other major illnesses were randomly assigned to active aspirin (100 mg on alternate days), active vitamin E (600 IU on alternate days), both active agents, or both placebos. Baseline information was self-reported and was collected by a mailed questionnaire that asked about a large number of vascular risk factors and lifestyle variables. All participants provided written informed consent and the Institutional Review Board and Brigham and Women's Hospital approved the WHS. Twice in the first year and yearly thereafter, participants were sent follow-up questionnaires asking about study outcomes, personal characteristics, medical history, and health habits. For this analysis, we included follow-up information from study entry through March 31, 2007. As of this date, follow-up was 97% complete.

Before randomization, blood samples were collected in tubes containing EDTA from 28,345 participating women and stored in vapor phase liquid nitrogen (-170°C). Samples were analyzed for lipids and a panel of inflammatory biomarkers. Total cholesterol was assayed with the use of reagents from Roche Diagnostics (Basel, Switzerland) and analyses could be performed on 27,939 of the blood samples.

Assessment of migraine. Participants were asked on the baseline questionnaire: "Have you ever had migraine headaches?" and "In the past year, have you had migraine headaches?" From this information, we categorized women into "no migraine his-

tory" and "any history of migraine." Furthermore, we distinguished between "active migraine," which includes women with self-reported migraine in the year prior to completing the baseline questionnaire, and "prior migraine," which includes women who reported ever having had a migraine but none in the year prior to completing the questionnaire. Participants who reported active migraine were asked about migraine-specific features, including migraine frequency. Answer categories for migraine frequency included < 6 times per year, every other month, monthly, weekly, and daily. From this information, we a priori recategorized migraine frequency into $< \text{monthly}$, monthly , and $\geq \text{weekly}$.

In previous studies of the WHS,^{10,17} we have shown good agreement with 1988 International Headache Society criteria for migraine.¹⁸ Specifically, we showed that among WHS participants who provided a blood sample and reported active migraine, 83.5% fulfilled all but one International Classification of Headache Disorders-I criteria (code 1.7, migrainous disorder) and 46.6% fulfilled all IHS criteria for migraine (code 1.1, migraine without aura).¹⁰ In addition, we have shown¹⁹ that in a subsample of the WHS, over 87% of women with self-reported active migraine could be diagnosed with migraine without aura (71.5%) or probable migraine without aura (16.2%) according to International Classification of Headache Disorders-II criteria.²⁰

Participants who reported active migraine were further asked whether they had an "aura or any indication a migraine is coming." Responses were used to classify women who reported active migraine into active migraine with aura and active migraine without aura.

Cardiovascular events. All participants were followed for the occurrence of the endpoint major CVD, a combined endpoint defined as the first of any of these events: nonfatal MI, nonfatal ischemic stroke, or ischemic cardiovascular death. In addition, we evaluated any first MI, ischemic stroke, coronary revascularization procedure (includes reports of coronary artery bypass grafts or percutaneous coronary angioplasty), and angina. There were too few cases of cardiovascular death to perform meaningful stratified analyses. Medical records were obtained for all reported cardiovascular endpoints except angina and reviewed by an Endpoints Committee of physicians. Nonfatal stroke was confirmed if the participant had a new focal-neurologic deficit of sudden onset that persisted for > 24 hours and was then classified as ischemic, hemorrhagic, or undefined with excellent inter-observer agreement.²¹ For this report, we only included ischemic stroke cases, and participants with other stroke subtypes were censored at the time of event. The occurrence of MI was confirmed if symptoms met World Health Organization criteria and if the event was associated with abnormal levels of cardiac enzymes or abnormal electrocardiograms. Deaths were confirmed by autopsy reports, death certificates, medical records, and information obtained from next of kin or family members and classified according to its specific cause.

Statistical analyses. Of the 27,939 women with completed blood assays, we excluded 79 with missing information on migraine status, 20 women who reported angina prior to receiving the baseline questionnaire, and 42 with missing information on migraine frequency, leaving 27,798 women free of CVD or angina at study entry for this analysis. We compared the baseline characteristics of participants with respect to migraine frequency status using analysis of covariance for continuous measurements, adjusting for age. We used direct standardization to adjust categorical variables for age in 5-year increments.

Table 1 Baseline characteristics according to migraine frequency in the Women's Health Study (n = 27,798)

	No history of migraine (n = 22,715)	History of migraine* (n = 1,515)	Active migraine, frequency			p†
			< Monthly (n = 2,685)	Monthly (n = 703)	≥ Weekly (n = 180)	
Mean age, y (SE)	54.9 (0.05)	55.5 (0.18)	53.0 (0.14)	52.0 (0.27)	53.1 (0.53)	<0.001
Mean body mass index, kg/m ² (SE)	25.9 (0.03)	26.1 (0.13)	26.2 (0.10)	25.6 (0.19)	25.5 (0.37)	0.006
Mean total cholesterol, mg/dL‡ (SE)	211.4 (0.27)	214.8 (1.05)	213.3 (0.79)	212.0 (1.55)	210.6 (3.05)	0.006
History of hypertension,§ %	24.6	30.2	25.8	24.4	31.5	<0.001
Smoking, %						
Never	51.2	50.5	54.1	56.1	57.8	<0.001
Past	37.0	35.4	35.8	36.3	33.6	
Current	11.8	14.1	10.1	7.6	8.6	
Alcohol consumption, %						
Rarely/never	43.5	45.0	46.8	49.0	56.9	<0.001
1-3 drinks/mo	13.1	14.2	14.7	12.7	17.1	
1-6 drinks/wk	32.7	30.5	30.5	30.5	21.2	
≥1 drink/d	10.8	10.3	8.0	7.8	4.8	
Physical activity, %						
Rarely/never	37.0	39.2	39.0	38.5	39.9	<0.001
<1/wk	19.2	20.1	21.8	19.7	19.0	
1-3/wk	32.3	29.5	29.3	30.2	34.1	
≥4/wk	11.6	11.3	9.9	11.6	7.1	
Postmenopausal hormone therapy, %						
Never	49.6	46.0	42.2	45.3	33.9	<0.001
Past	8.7	10.4	9.5	7.0	8.2	
Current	41.7	43.6	48.3	47.7	58.0	
Family history of myocardial infarction before age 60 y, %	11.4	12.4	12.6	11.4	9.0	0.30

*Women with history of migraine but no active migraine in the year before completing the baseline questionnaire.

†p Values from analysis of covariance for continuous or Mantel-Haenszel test for categorical variables.

‡To convert cholesterol values to millimoles per liter, multiply by 0.02586.

§Systolic blood pressure ≥140 mm Hg, diastolic blood pressure ≥90 mm Hg, physician-diagnosed hypertension, or antihypertensive treatment.

We used age-adjusted and multivariable-adjusted Cox proportional hazards models to calculate hazard ratios (HRs) and 95% confidence intervals (CIs) of the association between migraine frequency categories and CVD outcomes. In the multivariable models, we adjusted for age (continuous), history of hypertension (defined as systolic blood pressure ≥140 mm Hg, diastolic blood pressure ≥90 mm Hg, or physician diagnosis of hypertension, or antihypertensive treatment), body mass index (<25, 25–29.9, ≥30 kg/m²), smoking status (never, past, current), total cholesterol (quartiles), postmenopausal hormone use (never, past, current), and family history of MI prior to age 60 (yes, no). We incorporated a missing value indicator variable if the number of women with missing information was ≥100 or otherwise reassigned values of the reference group or past-user group, as applicable. Additional adjustment for alcohol consumption and exercise levels did not substantially change the effect estimates. Further, adjusting for randomized treatment assignments did not lead to different results.

In further analyses, we evaluated whether the association of migraine frequency and CVD outcomes was modified by migraine aura status. We evaluated statistically significant effect modification by using the likelihood ratio test. All analyses were performed using

SAS version 9.1 (SAS Inc, Cary, NC); p values were two-tailed and a p < 0.05 was considered statistically significant.

RESULTS Of the 27,798 women in this analysis, 5,083 (18.3%) reported any history of migraine, of whom 3,568 (70.2%) reported active migraine. Among active migraineurs, 75.3% reported a migraine frequency of < monthly, 19.7% monthly, and 5.0% ≥ weekly. In table 1, we summarize the association between migraine frequency and baseline characteristics. Women with a migraine frequency of at least weekly tended to have lower cholesterol values, smoked less and drank less alcohol, and were more likely to have a history of hypertension and to have a history of postmenopausal hormone use as women with a migraine frequency of less than monthly.

During a mean of 11.9 years of follow-up (329,704 person-years), a total of 706 major CVD

Table 2 Associations between migraine frequency and cardiovascular disease (CVD) in the Women's Health Study (n = 27,798)

	No history of migraine (n = 22,715): Referent	History of migraine* (n = 1,515): HR (95% CI)	Active migraine, frequency		
			< Monthly (n = 2,685): HR (95% CI)	Monthly (n = 703): HR (95% CI)	≥ Weekly (n = 180): HR (95% CI)
Major CVD† (n = 706)	n = 567	n = 48	n = 78	n = 7	n = 6
Age-adjusted	1.00	1.22 (0.91-1.63)	1.52 (1.20-1.93)	0.60 (0.29-1.28)	1.74 (0.78-3.89)
Multivariable-adjusted‡	1.00	1.13 (0.84-1.51)	1.55 (1.22-1.97)	0.65 (0.31-1.38)	1.93 (0.86-4.33)
Myocardial infarction (n = 305)	n = 243	n = 20	n = 38	n = 2	n = 2
Age-adjusted	1.00	1.18 (0.75-1.87)	1.65 (1.17-2.32)	0.38 (0.09-1.51)	1.29 (0.32-5.18)
Multivariable-adjusted‡	1.00	1.10 (0.70-1.73)	1.68 (1.19-2.37)	0.41 (0.10-1.67)	1.53 (0.38-6.15)
Ischemic stroke (n = 310)	n = 257	n = 16	n = 29	n = 4	n = 4
Age-adjusted	1.00	0.89 (0.54-1.47)	1.27 (0.86-1.86)	0.79 (0.29-2.13)	2.60 (0.97-6.97)
Multivariable-adjusted‡	1.00	0.80 (0.48-1.33)	1.28 (0.87-1.89)	0.84 (0.31-2.26)	2.77 (1.03-7.46)
Coronary revascularization§ (n = 655)	n = 530	n = 48	n = 67	n = 7	n = 3
Age-adjusted	1.00	1.32 (0.98-1.77)	1.27 (0.98-1.63)	0.55 (0.26-1.17)	0.85 (0.27-2.64)
Multivariable-adjusted‡	1.00	1.22 (0.90-1.63)	1.26 (0.97-1.63)	0.60 (0.28-1.26)	0.93 (0.30-2.89)
Angina (n = 418)	n = 322	n = 41	n = 48	n = 4	n = 3
Age-adjusted	1.00	1.84 (1.33-2.55)	1.49 (1.10-2.02)	0.52 (0.19-1.40)	1.39 (0.45-4.33)
Multivariable-adjusted‡	1.00	1.70 (1.23-2.36)	1.48 (1.09-2.02)	0.56 (0.21-1.51)	1.53 (0.49-4.78)

*Women with history of migraine but no active migraine in the year before completing the baseline questionnaire.

†A major CVD event was defined as the first of any of these events: nonfatal ischemic stroke, nonfatal myocardial infarction, or death from ischemic cardiovascular cause.

‡Adjusted for age, history of hypertension, smoking, body mass index, total cholesterol, postmenopausal hormone use, and family history of myocardial infarction before age 60 y.

§Includes reports of coronary artery bypass grafting or percutaneous coronary angioplasty.

events (nonfatal MI, nonfatal ischemic stroke, or death from ischemic CVD) occurred, which, taking into account the potential for multiple events in a single individual, included 305 first MIs, 310 ischemic strokes, and 151 CVD deaths. In addition, 655 women had coronary revascularization procedures and 418 women reported angina. In table 2, we summarize the age-adjusted and multivariable-adjusted association between migraine frequency and incident major CVD, MI, and ischemic stroke. Compared with women without a history of migraine, we found J-shaped associations between migraine frequency and major CVD, a finding driven by ischemic strokes. In multivariable-adjusted models, the HRs (95% CIs) for major CVD were 1.55 (1.22–1.97; $p < 0.001$), 0.65 (0.31–1.38; $p = 0.27$), and 1.93 (0.86–4.33; $p = 0.11$) for a migraine frequency of < monthly, monthly, and ≥ weekly, respectively. Women who reported a history of migraine but no active migraine in the year before completing the baseline questionnaire had a HR of 1.13 (0.84–1.51; $p = 0.43$). While we found increased relative risks for the outcomes MI and ischemic stroke in the high-migraine and low-migraine frequency group, the emphasis differed. Among women with active migraine,

we observed the strongest association with MI in the lowest migraine frequency category (HR = 1.68; 95% CI = 1.19–2.37; $p = 0.003$), while the strongest association for ischemic stroke was found in the high-migraine frequency group (HR = 2.77; 95% CI = 1.03–7.46; $p = 0.04$). We found no significant association between migraine frequency and coronary revascularization. For angina, we found the strongest association among women with prior migraine (HR = 1.70; 95% CI = 1.23–2.36; $p = 0.001$) but also for women with active migraine and a migraine frequency of < monthly (HR = 1.48; 95% CI = 1.09–2.02; $p = 0.01$).

When we took migraine aura status into account, we only observed a significant association between migraine frequency and CVD for women with migraine with aura (table 3; p for interaction = 0.009). We found strong and significant association with all ischemic vascular events among women with active migraine with aura with a low migraine frequency (< monthly), ranging from a HR of 1.81 (95% CI = 1.30–2.50; $p < 0.001$) for coronary revascularization to 2.43 (95% CI = 1.58–3.74; $p < 0.001$) for MI. For women with active migraine with aura and a migraine frequency of at least one per week, we only

Table 3 Multivariable-adjusted* associations between migraine frequency and cardiovascular disease (CVD) for women with active migraine, stratified by migraine aura status in the Women's Health Study (n = 27,798)

	Active migraine, frequency					
	< Monthly		Monthly		≥ Weekly	
	No.	HR (95% CI)	No.	HR (95% CI)	No.	HR (95% CI)
Migraine without aura (n = 2,140)		n = 1,590		n = 453		n = 97
Major CVD† (n = 37)	30	1.02 (0.71–1.48)	4	0.61 (0.23–1.63)	3	1.89 (0.61–5.88)
Myocardial infarction (n = 17)	15	1.14 (0.67–1.92)	1	0.34 (0.05–2.41)	1	1.42 (0.20–10.15)
Ischemic stroke (n = 15)	11	0.84 (0.46–1.53)	3	1.04 (0.33–3.27)	1	1.36 (0.19–9.69)
Coronary revascularization‡ (n = 33)	28	0.88 (0.60–1.30)	3	0.42 (0.13–1.29)	2	1.13 (0.28–4.53)
Angina (n = 27)	22	1.16 (0.75–1.80)	3	0.68 (0.22–2.12)	2	1.92 (0.48–7.71)
Migraine with aura (n = 1,428)		n = 1,095		n = 250		n = 83
Major CVD† (n = 54)	48	2.28 (1.70–3.07)	3	0.72 (0.23–2.25)	3	1.98 (0.64–6.17)
Myocardial infarction (n = 25)	23	2.43 (1.58–3.74)	1	0.53 (0.08–3.81)	1	1.64 (0.23–11.72)
Ischemic stroke (n = 22)	18	1.90 (1.18–3.08)	1	0.53 (0.07–3.77)	3	4.25 (1.36–13.29)
Coronary revascularization‡ (n = 44)	39	1.81 (1.30–2.50)	4	0.89 (0.33–2.39)	1	0.69 (0.10–4.88)
Angina (n = 28)	26	1.93 (1.29–2.89)	1	0.37 (0.05–2.65)	1	1.09 (0.15–7.76)

Models include an indicator variable for women who reported a history of migraine but not active migraine in the year before completing the baseline questionnaire. Women without a history of migraine serve as the reference group. Effect estimates and number of events for women with a history of migraine or without a history of migraine are listed in table 2.

*Adjusted for age, history of hypertension, smoking, body mass index, total cholesterol, postmenopausal hormone use, and family history of myocardial infarction before age 60 y.

†A major cardiovascular event was defined as the first of any of these events: nonfatal ischemic stroke, nonfatal myocardial infarction, or death from ischemic cardiovascular cause.

‡Includes reports of coronary artery bypass grafting or percutaneous coronary angioplasty.

found significant association with ischemic stroke (HR = 4.25; 95% CI = 1.36–13.29; $p = 0.01$).

DISCUSSION In this large, prospective cohort of women aged ≥ 45 years, we found particular patterns of associations between migraine frequency among active migraineurs and specific CVD events. The association with major CVD appeared J-shaped with increased risks for < monthly and \geq weekly attacks, a pattern also seen for stroke. The association with MI and angina showed a U-shaped association pattern. When we stratified by migraine aura status, we found no significant associations between migraine frequency and any ischemic vascular event among women with migraine without aura. In contrast, we found strong and significant associations between low migraine frequency (< monthly) and major CVD among women with active migraine with aura. In addition, women with active migraine with aura with a migraine frequency of at least weekly had over fourfold increased risk for ischemic stroke but not for any other ischemic vascular event.

The association between migraine frequency and CVD has previously only been evaluated for the outcome ischemic stroke. One study compared 86 women aged 20–44 with ischemic stroke with 214 controls.⁵ The results showed that women with migraine with

aura with an initial migraine frequency of ≥ 13 per year had substantially increased risk of ischemic stroke (OR = 10.4; 95% CI = 2.18–49.4) while those with a migraine frequency of < 13 per year had an OR of 3.58 (95% CI = 0.86–14.8). The results of this study also suggested that an increase in migraine frequency had stronger associations with ischemic stroke than a decrease in migraine frequency.⁵ Another study found no changes of the association between change in migraine frequency and stroke, but this was limited to women who used oral contraceptives.²²

In a population-based case-control study among women aged 15 to 49 years, 386 cases of ischemic stroke were age-matched and ethnicity-matched with 614 controls and participants were classified according to migraine status and migraine aura status.⁹ Women with migraine with visual aura had increased risk of ischemic stroke that was only apparent for those with a migraine frequency of > 12 per year (adjusted OR = 1.7; 95% CI = 1.1–2.8) but not for those with less frequent migraine (OR = 0.9; 95% CI = 0.6–1.4). In a previous report of the WHS, we found no association between migraine frequency and ischemic stroke but, because of the lower number of outcome events, we only could dichotomize migraine frequency in < monthly and \geq monthly.⁷

The association between migraine and silent infarcts as well as white matter lesions was investigated in the CAMERA study. In this population-based study from the Netherlands, the risk of infarcts in the posterior circulation territory increased with increasing migraine frequency ($p_{\text{trend}} < 0.005$).²³ Compared with controls, the risk of infarcts was 9.3 times higher among participants with a migraine frequency of at least once per month. Similarly, a significant association between migraine and silent infarct-like lesions in the posterior circulation tended to be stronger with a higher migraine frequency (≥ 1 per month).²⁴

Our results of substantially increased risk for ischemic stroke for women with active migraine with aura and a high migraine frequency are in agreement with the results of the prior studies. It remains unclear whether the association between migraine frequency and ischemic stroke in these studies increases again with lower migraine frequency, because migraine frequency could only be dichotomized.

Our data have several strengths, including the large number of participants and outcome events, confirmed vascular events after medical record review, with the exception of angina, standardized assessment of migraine, and the relative homogenous nature of our cohort, which may reduce confounding.

Several limitations should be considered when interpreting our data. First and most importantly, while the number of outcome events was large in the overall group, there were only limited outcome events in subgroups. Thus, as in previous studies^{5,9,23,24} and despite statistical significance, our effect estimates carry some degree of uncertainty, which should caution strong conclusions. Second, we only assessed migraine frequency at baseline, thus we could not evaluate the association of change of patterns of migraine frequency with risk of CVD, an association suggested by another study.⁵ Third, migraine and migraine features were self-reported. While we have shown good agreement with 1988 International Headache Society criteria for migraine¹⁰ and excellent agreement between self-reported migraine and International Classification of Headache Disorders–II–based migraine classification in the WHS,¹⁹ misclassification is possible. However, due to the prospective nature of our data, such misclassification would likely yield an underestimation of observed associations. Fourth, despite control for a number of potential confounders in our analysis, residual confounding is possible since our study is observational. Finally, participants in our study were all ≥ 45 years of age, health professionals, and mostly Caucasian. Thus, generalizability to other populations may be limited.

While there are several hypothesis why migraine may be linked with CVD,¹⁴ the mechanisms explaining this association remain unclear. Increasing evidence suggests that this link is particularly strong among migraineurs with aura. For ischemic stroke, smoking and oral contraceptive use have been identified as additional modifying factors.^{4,6,9,22,25} Migraine frequency may be another modifying factor, although associations may be complex and differential patterns may exist for specific CVD events. Diametric associations have also been found for the link between migraine with aura and specific CVD events according to vascular risk status²⁶ and for the 677C>T polymorphism in the methylenetetrahydrofolate reductase gene.^{27,28} It may be plausible that migraine frequency interacts with other modifying factors, such as age or vascular risk. There is evidence that patients with active migraine have less severe arteriosclerosis,^{29,30} which may suggest that vascular health plays a role in migraine occurrence. It has to be established whether changes in migraine frequency associate with vascular functions and whether other modifying factors help to explain links between migraine frequency and CVD events. We had too few outcome events in subgroups to further evaluate this hypothesis. While overweight and obesity do not seem to be associated with migraine overall, body mass index has consistently been associated with migraine frequency^{31–33} and two studies suggest that this association may be U- or J-shaped.^{32,33} Since we have controlled for body mass index in our analysis, we believe that the association between migraine frequency and CVD is not strongly influenced by obesity.

If migraine per se would increase the risk of CVD, one would expect that an increase in the frequency would lead to further risk increase. The pattern of association of our data only supports this hypothesis for ischemic stroke. However, migraine frequency may not necessarily be a measure of migraine severity. In addition, since associations between migraine and vascular events are only found for migraine with aura in most studies, aura frequency rather than migraine frequency may be a better marker of further increased risk of CVD; such information was not available in our data or other studies. Further, since the 1-year prevalence of migraine and migraine frequency decreases with increasing age, migraine and migraine frequency patterns over time may also be of interest in predicting future CVD events.

Taken together, migraine with aura per se may not be sufficient to increase the risk of CVD but additional factors seem to be necessary. These additional factors include vascular risk factors,^{3,9,26} migraine frequency,^{5,9} gene variants,^{27,28} use of oral contraceptives,^{22,25} or smoking.^{4,9} Further, there is evidence that the mecha-

nisms leading to ischemic stroke or coronary events among migraineurs with aura differ.^{26,27} Thus, future studies are warranted to evaluate the association of migraine, migraine subforms, and migraine patterns with risk of vascular events.

AUTHOR CONTRIBUTIONS

T.K. had full access to all the data in the study and takes responsibility for the integrity of the data, the accuracy of the data analysis, and the decision to submit for publication. T.K. conceived and designed the study, analyzed the data, as well as drafted the manuscript. All authors interpreted the data, critically revised the draft for important intellectual content, and gave final approval of the manuscript to be published. J.E.B. obtained funding.

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